* Disclaimer- this is not all my work! -just want to say thanks to the 2014 wiki where I stole many of these objectives from (pretty much all except the last part plus a word here and there)- I added our new material at the end. Happy studying friends we’re almost done!
* 1.Be able to describe how polymorphism in genes could be responsible for adverse drug reactions
* **Pharmacogenetics:** The study of genetic variation that gives rise to differing responses to drugs. Usually involves study of one or a few genes
* **Pharmacogenomics:** Similar to pharmacogenetics, but involves the study of the entire genome
* **Ecogenetics:** The study of genetic variation that gives rise to differing responses to specific dietary, chemical, and physical agents encountered in the environment
  + Differing genetics encode for differing proteins which interact/metabolize drugs with differing affinities and at different rates.
* 2. Be able to describe why the response to drugs can show a unimodal frequency distribution, as opposed to bi- or trimodal.
  + Unimodal Population Frequency DistributionsIndicate
    - involvement of many factor in altering drug response
    - Mostly multifactorial; Inheritance is probably polygenic
  + Bimodal Population Frequency Distribution
    - Indicate a single factor has major impact on drug response
    - There are more rare, but easier to identify
    - Associated with a single gene (i.e. Mendelian inheritance)
  + Trimodal distribution
    - is characteristic of traits showing incomplete dominance
* 3. Describe how genetic polymorphisms can influence pharmacokinetic properties of a drug, especially a drug’s Phase I and/or II metabolism and distribution.
  + Differences in Pharmacokinetics can occur at levels of:  
     • Absorption • Distribution  
     • Metabolism • Excretion
  + **Metabolism**
    - Phase I Metabolism: oxidation, reduction, hydroxylation of substrates
    - Phase II Metabolism: Conjugation reactions (glucouronidation, sulfation, etc)
      * Overall goal: ↑ drug’s solubility so it can be easily excreted
* **Pharmacogenetics of Phase I Metabolism Gene Products**
  + Pharmacogenetics of CYP2D6
    - Variances in this gene affect metabolism of: codeine, dextromethorphan, metoprolol
    - 5-10% of whites have trouble metabolizing these drugs
    - 75 known alleles exhibiting autosomal recessive inheritance
    - Debrisoquin
      * Metabolism shows trimodal distribution (incmplt. dom.)-Ultrafast, extensive, and poor
    - Nortriptyline
      * Some ultra-fast metabolizes of nortriptyline express multiple copies of CYP2D6 Gene
      * If patient expresses too many copies of the gene, it may be difficult to achieve a therapeutic bioavailability
  + Pharmacogenetics of Butyrylcholinesterase (*CHE1*)
    - Deficiency of this enzyme → prolonged paralysis / no breathing after succinylcholine administration
    - Autosomal recessive, at least 10 alleles
    - Homozygotes for recessive allele causes Butyrylcholinesterase deficiency
* **Pharmacogenetics of Phase II Metabolism Gene Products**
  + Pharmacogenetics N-Acetyltransferase 2 (*NAT2*)
    - Genetic variation in *NAT2* is common
    - Slow (poor) metabolizing phenotype → ↑ t1/2­ & Conc.Serum of drugs such as isoniazide, hydralazine, and procainamide, which can cause toxicities
    - Slow metabolizing phenotype has autosomal recessive phenotype, which has high incidence in white Americans and individuals of Zimbabwean ancestry
  + Pharmacogenetics of Thiopurine S-Methyltransferase (*TPMT*)
    - This enzyme typically metabolizes drugs used as immunosuppressants or anti-neoplastics (mercaptopurine, azothipurine, etc)
    - Whites show a trimodal distribution of activity (incomplete/partial dominance)
    - If homozygous for low-activity allele, then patient will increased risk of adverse drug reaction (ADR) if given standard dose of mercaptopurine
* 4. Describe how genetic polymorphisms can influence the pharmacodynamic properties of a drug, especially regarding how varying receptors can influence drug response
  + Pharmacogenetic variation in response to drugs is most pronounced in drugs which have a very narrow therapeutic index
  + Pharmacogenetics of P-Glycoprotein Transporter (*ABCB1/MDR1*)
    - This transporter typically acts to efflux substrates in an ATP-dependent manner
    - Strong linkage disequilibrium between two SNPs in the gene, so it is unknown which SNP is responsible for differences in phenotype
* Pharmacogenetics of β1-Adrenergic Receptor (*ADRB1*)
  + Activation of this receptor typically results in ↑ rate/strength of heart contractions, lipolysis, and renin release
  + Agonists to this receptor: isoproterenol, dobutamine (β-blockers)
  + Common variants: Arg-389 and Gly-389
  + ↑ evolutionary conservation of gene → ↑ affect of a polymorphism there
  + Variants in *ADRB1* gene serves as predictors of response to β-blocker (bucindolol) therapy for CHF
* Pharmacogenetics of Epidermal Growth Factor Receptor (*EGFR*)
  + ~10% patients treated with a tyrosine kinase inhibitor (Iressa) for NSC Lung Cancer showed improvement
  + Sequencing of this gene showed commonalities between the 10% of patients who responded favorably to this therapy regimen
    - It didn’t matter much though, as Iressa therapy showed no increase in overall survival
* 5. Be able to describe how genetic polymorphisms can influence an individual’s response to dietary/chemical/physical agents encountered in the environment
  + Dietary Ecogenetics of Glucose-6-Phos. DHD (*G6PD*)
    - G6PD is all over and is necessary for glutathione reduction and RBC membrane integrity
    - However, typically only very little G6PD is required to do these things
    - Some individuals carry mutant allele causing ↓G6PD and will have their already low levels of reduced glutathione eliminated upon ingesting Fava beans
    - These individuals are at a greatly increased risk for various oxidative cellular damage
  + Other Examples of Dietary Ecogenetics
    - Dietary Lactose
  + Dietary Folic Acid
  + Variants in *MTHFR*  can result in ↑ circulatory homocysteine
  + Inhaled Tobacco Smoke
    - α­1-antitrypsin deficiency can exacerbate already deleterious effects of smoke
  + UV Light
    - Allelic variants lead to albinism or defects in DNA repair enzymes and an increased susceptibility to skin cancers
* 6.Describe populations at higher risk of inheriting mutations that predispose individuals to differences regarding adverse drug events
  + check out the charts on page 936!
* 7. Describe how pharmacogentic/pharmacogenomic info is now beginning to be used to personalized medicine
  + Abacabir
    - In 2009 FDA ruled pt’s needing this anti-viral (reverse transcriptase inhibitor) for HIV tx, they must be genotyped beforehand
    - Pt’s carrying a specific HLA allele (HLA-B\*5701) can have a life threatening hypersensitivity rxn (HSR)
    - Prescreening reduces the HSR incidence from 7.8%-3.4%
  + Plavix (clopidogrel)
    - 25% of pts have sub-therapeutic anti-platelet response to plavix
    - CYP2C19 variant has been linked to impaired clopidogrel (a prodrug) metabolism
      * CYP2C19\*2, \*3, \*17 are all poor metabolizing allelic variants
    - If you know the pt’s genotype you can alter dosing and improve response to drug
  + Warfarin
    - Indentification of SNP (single nucleotide polymorphisms) have been used to guide warfarin dosing to prevent over anti-coagulation
      * CYP2C9
      * VKORC1
    - Pt’s who were genotyped before tx were hospitalized 30% less
* 8.Be able to integrate pharmacogenetic information and apply it to previously learned material: ya know all 900 other pages! ☺